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Case Report

A Japanese school urine screening program led to the diagnosis of *KCNJ11*-MODY: A case report

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Highlights

- A novel *KCNJ11* pathogenic variant was detected in a school-aged female.
- A school urine screening program contributed to early detection and diagnosis of MODY.
- Treatment with low-dose sulfonylurea was effective in this *KCNJ11*-MODY case.

Abstract. Although *KCNJ11* mutation is the main cause of neonatal diabetes mellitus, reports of maturity-onset diabetes in the young (MODY) related to *KCNJ11* are rare. Here, we report a case of *KCNJ11*-MODY in a 12-yr-old Japanese female. Hyperglycemia was initially detected during a school urine screening program. Subsequent laboratory examinations revealed impaired insulin secretion; however, no islet autoantibodies were detected. Genetic testing of *KCNJ11* revealed a novel heterozygous variant, c.153G>C, p.Glu51Asp. The patient's father had the same mutation and was diagnosed with diabetes at 46 yr of age. *KCNJ11*-MODY was suspected, and sulfonylurea administration resulted in adequate glycemic control in the patient. The American College of Medical Genetics and Genomics guidelines classify this variant as likely pathogenic, and the effectiveness of sulfonylureas supports its pathogenicity. The patient could be treated with 0.02–0.03 mg/kg/d of glibenclamide, as this mutation may be responsive to only a small amount of sulfonylurea. A detailed family history and sequencing of causative genes, including *KCNJ11*, may help diagnose diabetes in school-aged patients.

Key words: maturity onset diabetes of the young (MODY), *KCNJ11*, sulfonylurea therapy

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Introduction

Maturity-onset diabetes of the young (MODY) is characterized by the onset of hyperglycemia and impaired insulin secretion without insulin intolerance or obesity in younger patients (1). *KCNJ11*-MODY is caused by pathogenic variants of the *KCNJ11* gene and can often be successfully treated with sulfonylureas (SU) (2). Neonatal diabetes mellitus (NDM) caused by *KCNJ11* variants has been extensively reported; however, reports of *KCNJ11*-MODY are rare (3, 4) and *KCNJ11*-MODY has not been previously reported in school-aged Japanese children. Herein, we report a case of *KCNJ11*-MODY in a 12-yr-old, school-aged Japanese female in whom glucosuria was initially detected during a school urine screening program. Subsequently, the patient was switched from insulin to SU therapy.

Case Report

A 12-yr-old Japanese female presented to our hospital after the detection of glucosuria during a school urine screening program. The patient had not experience thirst, polydipsia, or weight loss. Her height, weight, and body mass index were 153.1 cm (+ 0.5 SD), 50.15 kg (+ 0.9 SD), and 21.4 kg/m^2 (+ 0.97 SD), respectively. Physical examination results were unremarkable and *A. nigricans* was not present. Laboratory tests revealed a hemoglobin A1c (HbA1c) level of 7.8%, and screenings for anti-glutamic acid decarboxylase (GAD) antibody, anti-insulin autoantibody, and anti-insulinoma-associated antigen-2 (IA-2) antibody were all negative. Other biochemical markers were within normal limits, with no accompanying hyperlipidemia or fatty liver observed on ultrasonography. The oral glucose tolerance test led to a diagnosis of diabetes, where the homeostasis model assessment for insulin resistance was 4.1, the homeostasis model assessment for β-cell function was 45.9%, and the insulinogenic index was 0.057, indicating a decreased insulin secretion capacity (**Table 1**). Her paternal grandfather had been diagnosed with diabetes in his 30s or 40s. Her 43-yr-old father did not have diagnosed diabetes; however, his HbA1c level was slightly elevated (6.0%) during a routine health checkup. Although MODY was suspected, *HNF4A*, *GCK*-, *HNF1A*-, and *HFN1B*-MODY were ruled out, because no mutations or deletions were found in *HNF4A*, *GCK*, *HNF1A*, or *HFN1B* per results of PCR-direct sequencing and multiplex ligation-dependent probe amplification. Slowly progressive type 1 diabetes was suspected and treatment with self-injected insulin was initiated. However, anti-GAD and anti-IA-2 antibodies remained negative six months and one year after the initial visit, respectively. Eight months later, an oral glucose tolerance test revealed a fasting C-peptide level of 1.5 ng/dL, suggesting that insulin secretion was maintained. The patient's HbA1c level remained stable, at approximately 7%, with a basal-bolus insulin regimen and carbohydrate count (5 units of insulin degludec and a carbohydrate insulin ratio of 33 g/U).

The patient's clinical course indicated the presence of other types of MODY, prompting us to perform additional genetic sequencing of *KCNJ11* and *INS*. Whole-exon Sanger sequencing revealed a novel heterozygous variant, c.153G>C (p.Glu51Asp), in *KCNJ11*. Therefore, *KCNJ11*-MODY was suspected and the initial insulin treatment was stopped, in favor of SU for treatment. The glucagon tolerance test after SU initiation revealed sufficient insulin secretion (**Fig. 1**), and her insulinogenic index, calculated using the oral glucose tolerance test, improved from 0.057 at onset to 0.47 after SU initiation (**Table 2**). Glibenclamide was initially started at a dosage of 0.02 mg/kg/d, and later increased to 0.03 mg/kg/d. Adequate glycemic control was maintained with HbA1c levels primarily below 7% with SU treatment for one year. Genetic analysis of the patient's father revealed a similar variant. Subsequently, his HbA1c level increased to 6.5%, and he was diagnosed with diabetes at 46 yr of age.

Informed consent was obtained from the patient and her parents for the publication of this case report.

Discussion

In pancreatic beta cells, insulin secretion is initiated when ATP-sensitive potassium (K_{ATP}) channels are closed and inhibited when they are open. This channel is an octameric complex of four pore-forming, inwardly rectifying potassium channel subunits (Kir6.2) encoded by *KCNJ11* and four regulatory sulfonylurea-receptor subunits (SUR1). Pathogenic variants of *KCNJ11* cause decreased insulin secretion from pancreatic beta cells by conferring reduced ATP sensitivity, resulting in a gain of channel function (5). The cell membrane remains

Table 1. The oral glucose tolerance test at onset revealed obviously decreased insulin secretion capacity

	Blood glucose (mg/dL)	Immunoreactive insulin (μU/mL)	C-Peptide immunoreactivity (ng/mL)
0 min	150	11.1	1.8
30 min	215	14.8	2.3
60 min	282	20.4	3.2
120 min	277	27.0	3.9
180 min	261	22.0	3.7

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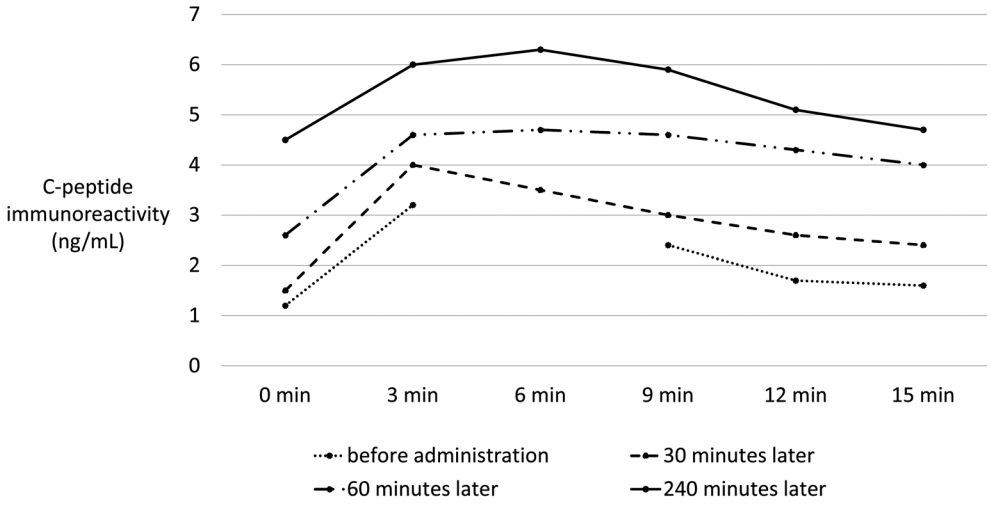

Fig. 1. Glucagon tests were performed consecutively before administration, and at 30, 60, and 240 min after administering 0.02 mg/kg of glibenclamide. Insulin secretion increased over time, and an adequate response was observed at 240 min after administration. Some data before administration is missing due to a technical error.

Table 2. The oral glucose tolerance test after administrating glibenclamide showed improved insulin secretion

	Blood glucose (mg/dL)	Immunoreactive insulin (μU/mL)	C-Peptide immunoreactivity (ng/mL)
0 min	137	12.6	2.6
30 min	232	57.7	6.4
60 min	216	60.1	7.8
120 min	165	43.9	7.1
180 min	165	43.0	6.7

hyperpolarized, leading to varying degrees of glucose metabolic abnormalities, including NDM and *KCNJ11*-MODY (6).

Here, we report a novel *KCNJ11* variant, c.153G>C (p.Glu51Asp), in a 12-yr-old patient with diabetes. The variant was located in the well-established functional domain of *KCNJ11*, but not found in the control database (gnomAD); the variant co-segregates with MODY in multiple affected family members. Another missense variant of the fifty-first amino acid residue of *KCNJ11* (p.Glu51Gly) has been reported as a pathogenic variant that can lead to NDM (7). According to the American College of Medical Genetics and Genomics (ACMG), this variant is "likely to be pathogenic" (PM1+PM2+PM5+PP1) (8). Additionally, in silico analysis evaluated this variant as "probably damaging" (score of 0.993 by Polymorphism Phenotyping version 2) (9). The 51st amino acid residue in *KCNJ11* (Glu51) is well-conserved across various species and consists of the slide helix of Kir 6.2, which plays an important role in translating conformational changes induced by ATP binding (10). Variants in the slide helix (p.Arg50Gly, p.Arg50Pro, p.Arg50Gln, p.Gly53Arg, and p.Tur62Arg) were considered pathogenic or likely pathogenic, suggesting the importance of this domain. Moreover, the remarkable response to SU therapy in this case suggests that *KCNJ11* c.153G>C (p.Glu51Asp) is a pathogenic variant.

In this report, *KCNJ11*-MODY was diagnosed in a 12-yr-old patient with diabetes, and her father, with the same *KCNJ11* variant, was later diagnosed with diabetes at the age of 46 yr. Her paternal grandfather, who developed diabetes in his 30s or 40s, potentially had *KCNJ11*-MODY. *KCNJ11* mutations are associated with various phenotypes on the diabetes spectrum. Among patients with *KCNJ11*-MODY, the age onset of diabetes varies widely from the teens to the 50s, even when affected by the same pathogenic variants (2, 4). This phenotypic spectrum of diabetes has also been reported among NDM patients with *KCNJ11* pathogenic variants, and non-genetic factors have been suggested to explain these differences (2). Although family history is an important predictor of *KCNJ11*-MODY, family members or relatives may not develop diabetes symptoms, even if they possess *KCNJ11* pathogenic variants. Regardless, when *KCNJ11*-MODY is suspected, any degree of glucose intolerance in relatives should be considered.

Many cases of diabetes caused by *KCNJ11* mutations have been effectively treated with SU (11, 12). SU binds to the SUR1 subunit of the mutant K_{ATP} channel, causing it to close and leading to membrane depolarization, which also allows insulin secretagogues,

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such as incretins, to augment insulin secretion (13). In patients with NDM resulting from KATP channel mutations, the required dosage also depends on the type of mutation (14, 15), and the transition to SU from insulin at an earlier age is associated with a higher success rate (15) and a lower required dosage of SU (16). In this case, the required SU dose was 0.02–0.03 mg/kg/d, which is close to the smallest SU dosage reported to date (13). This suggests that *KCNJ11* p.Glu51Asp could be controlled with low-dose SU or SU initiation in early life, allowing for a lower SU dosage for treatment.

The known side effects of SU include hypoglycemia and digestive disorders (14). However, a previous study reported that no patients discontinued SU treatment because of its side effects (11). Treatment with SU is considered safe and can improve the quality of life of patients with *KCNJ11*-MODY. Therefore, early identification and diagnosis of MODY is important and can be achieved through school urine screening programs.

Conclusion

We report a case of *KCNJ11*-MODY that was initially detected during a screening for glucosuria during a school urine screening program. The patient was successfully treated with SU. In school-aged patients with diabetes, obtaining a detailed family history and sequencing of the causative gene, including *KCNJ11*, may aid in specific diagnosis and lead to a better treatment strategy.

Conflict of interests: The authors have nothing to declare.

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References

1. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. Diabetes Care 2022;45(Suppl 1): S17–38. [CrossRef]
2. Bonnefond A, Philippe J, Durand E, Dechaume A, Huyvaert M, Montagne L, *et al*. Whole-exome sequencing and high throughput genotyping identified *KCNJ11* as the thirteenth MODY gene. PLoS One 2012;7: e37423. [Medline] [CrossRef]
3. Kitamyama K, Watanabe Y, Yamada Y, Higuchi S, Isaka Y, Motoyama K, *et al*. Effective management of hyperglycemia with relatively high-dose glibenclamide in a case of young-onset KATP-channel diabetes mellitus. J Japan Diab Soc 2022;65: 658–64 (in Japanese).
4. Yorifuji T, Nagashima K, Kurokawa K, Kawai M, Oishi M, Akazawa Y, *et al*. The C42R mutation in the Kir6.2 (*KCNJ11*) gene as a cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. J Clin Endocrinol Metab 2005;90: 3174–8. [Medline] [CrossRef]
5. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, *et al*. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350: 1838–49. [Medline] [CrossRef]
6. Chen Y, Hu X, Cui J, Zhao M, Yao H. A novel mutation *KCNJ11* R136C caused *KCNJ11*-MODY. Diabetol Metab Syndr 2021;13: 91. [Medline] [CrossRef]
7. De Franco E, Saint-Martin C, Brusgaard K, Knight Johnson AE, Aguilar-Bryan L, Bowman P, *et al*. Update of variants identified in the pancreatic β-cell K_{ATP} channel genes KCNJ11 and ABCC8 in individuals with congenital hyperinsulinism and diabetes. Hum Mutat 2020;41: 884–905. [Medline] [CrossRef]
8. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al*. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17: 405–24. [Medline] [CrossRef]
9. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, *et al*. A method and server for predicting damaging missense mutations. Nat Methods 2010;7: 248–9. [Medline] [CrossRef]
10. Antcliff JF, Haider S, Proks P, Sansom MS, Ashcroft FM. Functional analysis of a structural model of the ATP-binding site of the KATP channel Kir6.2 subunit. EMBO J 2005;24: 229–39. [Medline] [CrossRef]
11. Bowman P, Sulen Å, Barbetti F, Beltrand J, Svalastoga P, Codner E, *et al*. Neonatal Diabetes International Collaborative Group. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to *KCNJ11* mutations: an international cohort study. Lancet Diabetes Endocrinol 2018;6: 637–46. [Medline] [CrossRef]
12. Warncke K, Eckert A, Kapellen T, Kummer S, Raile K, Dunstheimer D, *et al*. Clinical presentation and long-term outcome of patients with *KCNJ11*/ABCC8 variants: Neonatal diabetes or MODY in the DPV registry from Germany and Austria. Pediatr Diabetes 2022;23: 999–1008. [Medline] [CrossRef]
13. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B, *et al*. Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006;355: 467–77. [Medline] [CrossRef]
14. Garcin L, Mericq V, Fauret-Amsellem AL, Cave H, Polak M, Beltrand J. Neonatal diabetes due to potassium channel mutation: Response to sulfonylurea according to the genotype. Pediatr Diabetes 2020;21: 932–41. [Medline] [CrossRef]

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15. Babiker T, Vedovato N, Patel K, Thomas N, Finn R, Männikkö R, *et al*. Successful transfer to sulfonylureas in *KCNJ11* neonatal diabetes is determined by the mutation and duration of diabetes. Diabetologia 2016;59: 1162–6. [Medline] [CrossRef]
16. Thurber BW, Carmody D, Tadie EC, Pastore AN, Dickens JT, Wroblewski KE, *et al*. United States Neonatal Diabetes Working Group. Age at the time of sulfonylurea initiation influences treatment outcomes in *KCNJ11*-related neonatal diabetes. Diabetologia 2015;58: 1430–5. [Medline] [CrossRef]